REMARKS

OUTSTANDING ISSUES:

- All claims stand rejected under 35 U.S.C. § 112(2).
- Claims 22-27 stand rejected under 35 U.S.C. §103(a), as being unpatentable over Galin or Iverson in combination with Bang and Esmon.
- Claims 28 and 29 stand rejected under 35 U.S.C. §103(a), as being unpatentable over Galin or Iverson in combination with Bang and Esmon, in further view of Stocker.

Applicants thank the Examiner for his thorough reading of the application. The following comments are directed toward the Office Action of January 13, 1997. Claims 22-29 are pending currently.

35 U.S.C. § 112, second paragraph

The Examiner rejects claims 22-29 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing particularly to point out and distinctly claim the subject matter which applicant regards as the invention.

First, the Examiner contends that the use of the phrase "effective dose" is indefinite, and that the function to be achieved should be recited after the phrase. Applicants have amended claim 22 herein as suggested helpfully by the Examiner. Claim 22 now reads "...administration of a pharmacologically effective dose of Protein C to reduce said intraocular inflammation...."

In addition, the Examiner states that he confused by the reference in claim 23 to "activated Protein C", and what that means as far as the "Protein C" of claim 22 is concerned.

Applicants submit that protein C is, in its natural, inactive, but that it does not matter whether the Protein C that is administered is active or inactive. Once Protein C is administered, it will be activated in the eye as the result of thrombin being released from the vasculature and complexing with thrombomodulin in the ocular tissues. This thrombin-thrombomodulin complex activates protein C from the inactive zymogen state; thus, this locally, ocular-generated thrombin drives the activation of protein C.

Applicants submit that the Protein C claimed in claim 22 can be either activated or inactivated as it is not necessary to the invention to have one form or the other, given the chemophysiology of the eye as described above. Claim 23, on the other hand, is drawn specifically to activated Protein C. However, Applicants contend that use of the phrase "activated Protein C" in claim 23 does not render either claim 22 or claims 23-29 indefinite.

In view of the amendment to claim 22 and the and remarks above, Applicants respectfully request that the rejection of claims 22-29 under 35 U.S.C. §112, second paragraph be withdrawn.

35 U.S.C. § 103

Claims 1-21 stand rejected under 35 U.S.C. §103 as being unpatentable over Galin or Iverson in combination with Bang and Esmon. This rejection is respectfully traversed.

Applicants contend that a person having ordinary skill in this art would not have had a reasonable expectation that protein C would have a pharmacological effect in the eye. It is now known that thrombin is

released from the vasculature and complexes to thrombomodulin--an endothelial-bound membrane receptor for thrombin--in ocular tissues. This thrombin-thrombomodulin complex activates protein C from an inactive zymogen state; thus, this locally-generated thrombin drives the activation of protein C should the administered protein C be inactive. The thrombin-thrombomodulin complex converts factor V to factor Va and factor VIII to factor Vllla, the preferred substrates for activated protein C, in exerting its antithrombotic effect. This pathway is demonstrated by the present invention. Prior to the filing of the present application, this role of thrombomodulin in ocular tissue had not been demonstrated. Thus, Applicants respectfully submit that there would have been no motivation to one of ordinary skill in this art to administer protein C for treatment of intraocular fibrin.

Additionally, delivery of therapeutic pharmaceuticals to the eye is not a trivial matter. In many instances, systemically administered drugs do not reach the eye in therapeutic levels, see e.g., Mindel JS: Pharmacokinetics, In Duane TD & Jaeger EA (eds). Biomedical Foundation of Ophthalmology, Volume 3, Philadelphia: JB Lippincott Co. (1988); and oral or intravenously administered antibiotics often fail to reach therapeutic concentrations in the cornea or within the eye itself, see Leopold IH: Chemotherapy of Infections, In Duane TD & Jaeger EA (eds). Biomedical Foundation of Ophthalmology, Volume 3, Philadelphia: JB Lippincott Co. (1988). It is a concern that systemic administration of drugs to achieve therapeutic ocular effects will trigger a toxic systemic reaction, as is the case with anticholinergics such as atropine, sympathomimetics such epinephrine, beta blockers such as timolol and parasympathomimetics such pilocarpine. Many drugs, if systemically administered in large

concentrations to achieve a desired result in the eye, would result in serious systemic dysfunction, side effects, and possibly death.

None of the references cited address the challenges of administration of drugs to the eye, or demonstrate that administration of Protein C would be effective in treating intraocular fibrin. None of the cited references disclose, teach or suggest in any form the use of protein C and/or protein S as ocular pharmacological agents to inhibit intraocular fibrin formation and inflammation as disclosed in the instant application.

In addition, the Examiner has rejected claims 28-29 as being unpatentable over Galin or Iverson in combination with Bang and Esmon, in further view of Stocker. Though Stocker discloses Protein S, Applicants submit that, as the arguments above detail, such disclosure does not teach the challenges of administration of drugs to the eye or that administration of active or inactive Protein C would be effective in treating intraocular fibrin.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination, *In re Bond*, 910 F.2d 831, 834 (Fed. Cir. 1990), *see also ACS Hospital Systems, Inc. v. Montefiori Hospital*, 732 F.2d 1572, 1577 (Fed. Cir. 1984); and "one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention", *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Applicants respectfully submit that the cited references do not render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 22-29 under 35 U.S.C. §103 be withdrawn.

This intended to be a complete response to the Final Office Action mailed January 13, 1997. Applicants respectfully submit that claims 22-29 are in condition for allowance. If it will facilitate the completion of prosecution of the present application, the Examiner is requested to call the undersigned attorney of record.

Respectfully submitted,

Sarah Brashears
Registration No. 38,087

Date: 6/13/97

MCGREGOR & ADLER, P.C.
8011 Candle Lane
Houston, Texas 77071
(713) 777-2321